Synthesis of 4*H*-Pyrazolo- and 4*H*-Pyrrolophenothiazin-4-one Derivatives

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5-Methyl- and 6-methyl-2-phenyl-2*H*-indazole-4,7-diones were condensed with 2-aminobenzenethiol or 6-substituted-3-aminopyridine-2(1*H*)thiones **4** to produce a new type of 5-methyl-2-phenyl-4*H*-pyrazolophenothiazin-4-ones or 8-substituted-7-aza-5-methyl-2-phenyl-4*H*-pyrazolophenothiazin-4-one derivatives. From 6-bromo-2,5-dimethyl-1,3-diphenyl-2*H*-isoindole-4,7-dione and **4** 8-substituted-7-aza-2,5-dimethyl-1,3-diphenyl-4*H*-pyrrolophenothiazin-4-one derivatives were also prepared.

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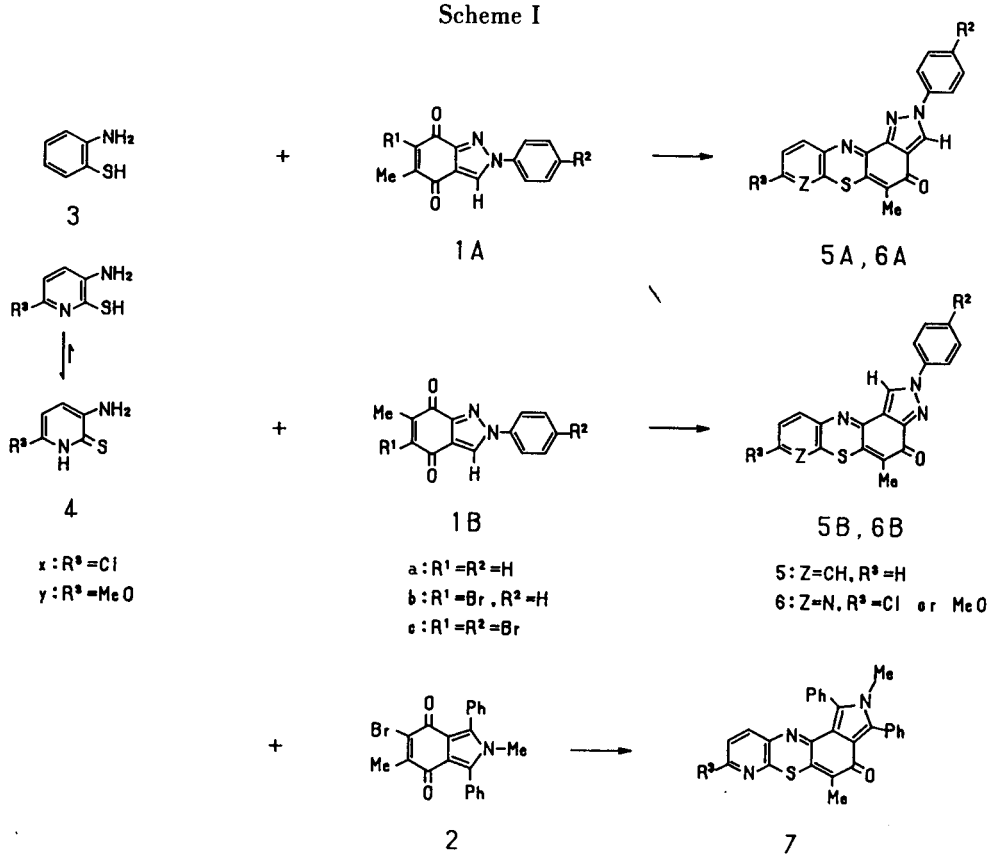
In continuation of our study for the synthesis of cyclic iminoquinone derivatives [1-7], we were interested in the reaction of 2*H*-isoindole-4,7-dione derivatives with 2-aminobenzenethiol giving two types of the condensation products [6].

In this paper, the preparation of a new type of 4*H*-pyrazolophenothiazin-4-ones and their azaphenothiazone derivatives by the reactions of 2*H*-indazole-4,7-dione derivatives **1** with 2-aminobenzenethiol (**3**) or 6-substituted 3-aminopyridine-2(1*H*)-thiones **4** are reported. From 6-bromo-2,5-dimethyl-1,3-diphenyl-2*H*-isoindole-4,7-dione (**2**) and **4**, a new type of 7-aza-4*H*-pyrrolophenothiazin-4-one derivatives **7** were also prepared.

The 1,3-dipolar cycloaddition of 3-phenylsydnone with *p*-toluquinone produced equimolar amounts of the regioisomers, 5-methyl- and 6-methyl-2-phenyl-2*H*-indazole-4,7-diones **1A** and **1B**. The structures of **1A** and **1B** were inferred from the X-ray crystallographic analysis carried out on the monobrominated product of **1A** [8]. An equimolar mixture of **1** and **3** or **4y** in ethanol was stirred at room

Scheme I



Table

Physical and Analytical Data for Compounds **5**, **6** and **7**

Compound	R^2	R^3	Yield (%)	MP (°C) [a]	Molecular Formula	Mass (M+) (Relative intensity %)	Elemental Analyses (%) Found/(Calcd.) C	H	N
5Aa	H	H	77	310-312	$C_{20}H_{13}N_3OS$ (343.4)	343 (100)	69.75 (69.95)	3.59 (3.82)	11.86 (12.24)
5Ac	Br	H	78	309-312	$C_{20}H_{12}BrN_3OS$ (422.3)	421/423 (93) (100)	56.98 (56.88)	2.78 (2.86)	9.59 (9.95)
5Ba	H	H	76	249-252	$C_{20}H_{13}N_3OS$ (343.4)	343 (100)	69.75 (69.95)	3.69 (3.82)	11.89 (12.24)
5Bc	Br	H	90	318-321	$C_{20}H_{12}BrN_3OS$ (422.3)	421/423 (94) (100)	57.10 (56.88)	2.91 (2.86)	9.61 (9.95)
6Aax	H	Cl	74	275 dec	$C_{19}H_{11}ClN_4OS$ (378.8)	378/380 (100) (40)	59.92 (60.24)	2.79 (2.93)	14.66 (14.79)
6Acx	Br	Cl	85	304 dec	$C_{19}H_{10}BrClN_4OS$ (457.7)	456/458/460 (77) (100) (32)	49.56 (49.86)	2.26 (2.20)	12.13 (12.24)
6Aay	H	MeO	87	320 dec	$C_{20}H_{14}N_4O_2S$ (374.4)	374 (100)	64.51 (64.16)	3.64 (3.77)	14.55 (14.96)
6Acy	Br	MeO	90	343 dec	$C_{20}H_{13}BrN_4O_2S$ (453.3)	452/454 (95) (100)	53.22 (52.99)	2.63 (2.89)	12.17 (12.36)
6Bax	H	Cl	86	309 dec	$C_{19}H_{11}ClN_4OS$ (378.8)	378/380 (100) (41)	60.01 (60.24)	2.87 (2.93)	14.55 (14.79)
6Bcx	Br	Cl	87	283-286	$C_{19}H_{10}BrClN_4OS$ (457.7)	456/458/460 (70) (100) (33)	49.78 (49.86)	2.46 (2.20)	12.04 (12.24)
6Bay	H	MeO	72	275-277	$C_{20}H_{14}N_4O_2S$ (374.4)	374 (100)	64.40 (64.16)	3.63 (3.77)	14.65 (14.96)
6Bcy	Br	MeO	94	305 dec	$C_{20}H_{13}BrN_4O_2S$ (453.3)	452/454 (96) (100)	53.25 (52.99)	2.68 (2.89)	12.14 (12.36)
7x	—	Cl	85	250-252	$C_{27}H_{18}ClN_3O_2S$ (468.0)	467/469 (100) (42)	69.21 (69.30)	3.95 (3.88)	8.75 (8.98)
7y	—	MeO	96	270-273	$C_{28}H_{21}N_3O_2S$ (463.6)	463 (100)	72.80 (72.55)	4.40 (4.57)	8.84 (9.06)

[a] Recrystallized from benzene.

temperature for several hours to afford 5-methyl-2-phenyl-4*H*-pyrazolophenothiazin-4-one derivatives **5** or 8-substituted 7-aza-5-methyl-2-phenyl-4*H*-pyrazolophenothiazin-4-one derivatives **6** in good yields. In the case of the reaction of *N*-(*p*-bromophenyl)-derivatives **1Ac** or **1Bc** with **4y** the products were obtained at higher temperature. The reactions of **1** and 3-amino-6-chloropyridine-2(1*H*)-thione (**4x**) were carried out with some modifications: to the mixture of **1Aa** or **1Ba** and **4x** in ethanol 6*N*-hydrochloric acid was added at room temperature and the mixture of **1Ac** or **1Bc**, **4x** and 6*N*-hydrochloric acid was refluxed.

In the nmr spectra, the characteristic singlet signals assignable to hydrogen at the 3-position of **1A** and **1B** shifted to lower magnetic field for the condensation products **5** and **6**, especially for **5B**.

The reactions investigated are summarized in Scheme I. The analytical and physical data for the compounds obtained in these reactions are listed in the Table.

EXPERIMENTAL

Melting points were determined on a Yanaco micromelting point apparatus and are uncorrected. The infrared spectra were taken on a JASCO A-102 spectrometer using potassium bromide pellets and the ultraviolet spectra were recorded with a JASCO UVIDEC-505 in chloroform solution. The nuclear magnetic resonance spectra were measured on a Varian XL-200 spectrometer in deuteriochloroform, using tetramethylsilane as the internal standard. Mass spectra were obtained with a Hitachi M-52 or ESCO EMD-05B spectrometer. For column chromatography, silica gel(Kiesel-gel 60, Merck, 70-230 mesh ASTM) was used.

General Method of Condensation of 2*H*-Indazole-4,7-dione (**1**) with 2-Aminobenzenethiol (**3**).

To a suspension of 0.5 mmole of **1** [8] in 10 ml of ethanol, 0.5 mmole of **3** was added and the mixture was stirred at room temperature for several hours. The resulting solid was filtered and was purified by the column chromatography with silica gel using benzene-chloroform (7:1) as the eluent.

5-Methyl-2-phenyl-4*H*-pyrazolo[5,4-*a*]phenothiazin-4-one (**5Aa**).

By the reaction of **1Aa** or **1Ab** with **3**, **5Aa** was produced as orange needles.

Compound **5Aa**.

This compound had ir: 1622 (C=O) cm^{-1}; uv: λ max, nm (log ε), 475 (3.95), 383 (3.98), 331 (4.18), 315 sh, 278 (4.48); ^1H nmr: δ 8.64 (s, 1H, pyrazole H), 8.11 (d, 1H), 7.96 (d, 2H), 7.64-7.41 (m, 6H), 2.20 (s, 3H, iminoquinone CH_3).

5-Methyl-2-(*p*-bromophenyl)-4*H*-pyrazolo[5,4-*a*]phenothiazin-4-one (**5Ac**).

From the reaction of **1Ac** and **3**, **5Ac** was obtained as red needles.

Compound **5Ac**.

This compound had ir: 1622 (C=O) cm^{-1}; uv: λ max, nm (log ε), 477 (3.97), 383 (3.99), 332 (4.23), 284 (4.53); ^1H nmr: δ 8.61 (s, 1H, pyrazole H), 8.09 (m, 1H), 7.84 (d, 2H), 7.69 (d, 2H), 7.49 (m, 2H), 7.38 (s, 1H), 2.19 (s, 3H, iminoquinone CH_3).

5-Methyl-2-phenyl-4*H*-pyrazolo[4,5-*a*]phenothiazin-4-one (**5Ba**).

By the reaction of **1Ba** or **1Bb** with **3**, **5Ba** was prepared as reddish orange needles.

Compound **5Ba**.

This compound had ir: 1635 (C=O) cm^{-1}; uv: λ max, nm (log ε), 467 (4.03), 389 (4.04), 351 sh (3.96), 333 sh (4.05), 284 (4.48); ^1H nmr: δ 9.26 (s, 1H, pyrazole H), 8.11 (d, 1H), 7.98 (d, 2H), 7.62-7.43 (m, 6H), 2.26 (s, 3H, iminoquinone (CH_3).

5-Methyl-2-(*p*-bromophenyl)-4*H*-pyrazolo[4,5-*a*]phenothiazin-4-one (**5Bc**).

From **1Bc** and **3**, **5Bc** was obtained as red needles.

Compound **5Bc**.

This compound had ir: 1627 (C=O) cm^{-1}; uv: λ max, nm (log ε), 468 (4.00), 388 (4.00), 353 sh (3.99), 353 sh, 287 (4.49); ^1H nmr: δ 9.56 (s, 1H, pyrazole H), 8.26 (m, 1H), 7.89 (d, 2H), 7.69 (d, 2H), 7.53 (m, 3H), 2.28 (s, 3H, iminoquinone CH_3).

7-Aza-5-methyl-8-methoxy-2-phenyl-4*H*-pyrazolo[5,4-*a*]phenothiazin-4-one (**6Aay**) and 7-Aza-5-methyl-8-methoxy-2-phenyl-4*H*-pyrazolo[4,5-*a*]phenothiazin-4-one (**6Bay**).

By the method described for preparation of compound **5**, **6Aay** and **6Bay** were obtained from **1Aa** and **1Ba** with **4y** [9] respectively.

Compound **6Aay**.

This compound had ir: 1630 (C=O) cm^{-1}; uv: λ max, nm (log ε), 471 (4.23), 388 (3.86), 357 (4.12), 341 (4.17), 328 sh (4.09), 281 (4.59); ^1H nmr: δ 8.66 (s, 1H, pyrazole H), 8.19 (d, 1H), 7.94 (d, 2H), 7.64-7.42 (m, 3H), 6.87 (d, 1H), 4.08 (s, 3H, OCH_3), 2.23 (s, 3H, iminoquinone CH_3).

Compound **6Bay**.

This compound had ir: 1638 (C=O) cm^{-1}; uv: λ max, nm (log ε), 466 (4.26), 396 sh, 360 (4.00), 343 (4.05), 329 (4.01), 282 (4.56), 267 sh (4.46); ^1H nmr: δ 8.78 (s, 1H, pyrazole H), 7.96 (m, 3H), 7.64-7.42 (m, 3H), 6.85 (d, 1H), 4.06 (s, 3H, OCH_3), 2.25 (s, 3H, iminoquinone CH_3).

7-Aza-5-methyl-8-methoxy-2-(*p*-bromophenyl)-4*H*-pyrazolo[5,4-*a*]phenothiazin-4-one (**6Acy**) and 7-Aza-5-methyl-8-methoxy-2-(*p*-bromophenyl)-4*H*-pyrazolo[4,5-*a*]phenothiazin-4-one (**6Bcy**).

The mixture of 0.5 mmole of **1Ac** (or **1Bc**) and 0.5 mmole of **4y** in 10 ml of ethanol was stirred under refluxing for 1.5 hours. After column chromatography on silica gel **6Acy** (or **6Bcy**) was obtained as reddish orange crystals.

Compound **6Acy**.

This compound had ir: 1633 (C=O) cm^{-1}; uv: λ max, nm (log ε), 473 (4.23), 388 (3.86), 359 (4.12), 343 (4.16), 284 (4.61); ^1H nmr: δ 8.59 (s, 1H, pyrazole H), 8.16 (m, 1H), 7.87 (m, 2H), 7.72 (m, 2H), 6.87 (d, 1H), 4.07 (s, 3H, OCH_3), 2.27 (s, 3H, iminoquinone CH_3).

Compound **6Bcy**.

This compound had ir: 1628 (C=O) cm^{-1}; uv: λ max, nm (log ε), 467 (4.25), 361 (3.98), 344 (4.03), 287 (4.53), 268 sh (4.41); ^1H nmr: δ 8.76 (s, 1H, pyrazole H), 7.96-7.80 (m, 2H), 7.68 (m, 2H), 7.39 (s, 1H), 6.85 (d, 1H), 4.06 (s, 3H, OCH_3), 2.25 (s, 3H, iminoquinone CH_3).

7-Aza-8-chloro-5-methyl-2-phenyl-4*H*-pyrazolo[5,4-*a*]phenothiazin-4-one (**6Aax**) and 7-Aza-8-chloro-5-methyl-2-phenyl-4*H*-pyrazolo[4,5-*a*]phenothiazin-4-one (**6Bax**).

From the reaction of **1Aa** (or **1Ba**) with **4x** [9] in the presence of 6*N* hydrochloric acid in a similar manner as for the preparation of compound **5** **6Aax** (or **6Bax**) was produced as orange red needles.

Compound **6Aax**.

This compound had ir: 1625 (C=O) cm^{-1}; uv: λ max, nm (log ε), 462 (4.07), 386 (3.99), 352 sh (4.10), 337 (4.18), 281 (4.58); ^1H nmr: δ 8.63 (s, 1H, pyrazole H), 8.20 (d, 1H), 7.91 (d, 2H), 7.64-7.46 (m, 3H), 7.41 (d, 1H), 2.20 (s, 3H, iminoquinone CH_3).

Compound **6Bax**.

This compound had ir: 1633 (C=O) cm^{-1}; uv: λ max, nm (log ε), 454 (4.16), 395 (4.09), 353 (4.07), 338 (4.11), 283 (4.59); ^1H nmr: δ 8.79 (s, 1H, pyrazole H), 7.97 (m, 3H), 7.63-7.38 (m, 4H), 2.26 (s, 3H, iminoquinone CH_3).

7-Aza-8-chloro-5-methyl-2-(*p*-bromophenyl)-4*H*-pyrazolo[5,4-*a*]phenothiazin-4-one (**6Acx**) and 7-Aza-8-chloro-5-methyl-2-(*p*-bromophenyl)-4*H*-pyrazolo[4,5-*a*]phenothiazin-4-one (**6Bcx**).

To an equimolar mixture of **1Ac** (or **1Bc**) and **4x** in ethanol was added 6*N* hydrochloric acid and stirred under refluxing for 2 hours. The resulting solid was filtered and chromatographed on silica gel column as described above.

Compound **6Acx**.

This compound had ir: 1637 (C=O) cm^{-1}; uv: λ max, nm (log ε), 463 (4.08), 387 (4.00), 353 (4.13), 338 (4.19), 286 (4.62); ^1H nmr: δ 8.60 (s, 1H, pyrazole H), 8.19 (d, 1H), 7.82 (d, 2H), 7.71 (d, 2H), 7.41 (m, 1H), 2.21 (s, 3H, iminoquinone CH_3).

Compound **6Bcx**.

This compound had ir: 1635 (C=O) cm^{-1}; uv: λ max, nm (log ε), 456 (4.11), 392 (4.03), 354 (4.08), 338 (4.13), 287 (4.59); ^1H nmr: δ 8.77 (s, 1H, pyrazole H), 7.97 (d, 1H), 7.90-7.69 (m, 4H), 7.41 (d, 1H), 2.25 (s, 3H, iminoquinone CH_3).

7-Aza-8-chloro- and 7-Aza-8-methoxy-2,5-dimethyl-1,3-diphenyl-4*H*-pyrrolo[3,4-*a*]phenothiazin-4-one (**7x** and **7y**).

An equimolar mixture of 6-bromo-2,5-dimethyl-1,3-diphenyl-2*H*-isoindole-4,7-dione (**2**), **4x** (or **4y**) and potassium acetate in ethanol-benzene was stirred under refluxing for 2-4 hours. By the column chromatography on silica gel using benzene as the eluent **7x** (or **7y**) was purified.

Compound **7x**.

This compound had ir: 1620 (C=O) cm^{-1}; uv: λ max, nm (log ε), 473 (4.27), 343 (4.15), 259 (4.61); ^1H nmr: δ 7.56 (s, 10H), 7.09 (d, 2H), 3.42 (s, 3H, NCH_3), 2.08 (s, 3H, iminoquinone CH_3).

Compound **7y**.

This compound had ir: 1612 (C=O) cm^{-1}; uv: λ max, nm (log ε), 479 (4.29), 366 sh (4.02), 347 (4.14), 259 (4.61); ^1H nmr: δ 7.57 (m, 10H), 7.13 (d, 1H), 6.59 (d, 1H), 3.97 (s, 3H, OCH_3), 3.43 (s, 3H, NCH_3), 2.10 (s, 3H, iminoquinone CH_3).

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REFERENCES AND NOTES

[1] S. Nan'ya, E. Maekawa, H. Hayakawa, Y. Kitaguchi and Y. Ueno, *J. Heterocyclic Chem.*, **22**, 1483 (1985).

[2] S. Nan'ya, E. Maekawa, W. Kang and Y. Ueno, *J. Heterocyclic Chem.*, **23**, 589 (1986).

[3] Y. Ueno, S. Nan'ya, H. Hayakawa, W. Kang and E. Maekawa, *Monatsh. Chem.*, **118**, 381 (1987).

[4] S. Nan'ya, E. Maekawa, W. Kang and Y. Ueno, *J. Heterocyclic Chem.*, **23**, 1697 (1986).

[5] H. Hayakawa, S. Nan'ya, T. Yamamoto, E. Maekawa and Y. Ueno, *J. Heterocyclic Chem.*, **23**, 1737 (1986).

[6] S. Nan'ya, T. Tange, E. Maekawa and Y. Ueno, *J. Heterocyclic Chem.*, **23**, 1267 (1986).

[7] W. Kang, S. Nan'ya, Y. Yamaguchi, E. Maekawa and Y. Ueno, *J. Heterocyclic Chem.*, **24**, 91 (1987).

[8] S. Nan'ya, K. Katsuraya, E. Maekawa, K. Kondo and S. Eguchi, *J. Heterocyclic Chem.*, **24**, 971 (1987).

[9] C. O. Okafor, *J. Org. Chem.*, **38**, 4383 (1973).